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Original Article

Respiratory Syncytial Virus Infection Outbreak Among Pediatric Patients With Oncologic Diseases and/or BMT

Sema Anak, MD,[1] Didem Atay, MD,[2]* Aysegul Unuvar, MD,[1] Mesut Garipardic, MD,[3] Leyla Agaoglu, MD,[1] Gulyuz Ozturk, MD,[1] Zeynep Karakas, MD,[1] and Omer Devecioglu, MD[1]

Summary. Background: Respiratory syncytial virus (RSV) has been reported to cause severe morbidity and mortality among cancer patients receiving chemotherapy with or without autologous/allogeneic hematopoetic stem cell transplantation (HSCT). There have been few reports describing the outcome of RSV infection specifically among pediatric oncology patients. Methods: Two RSV infection outbreaks developed between February–April 2006 and January–March 2009 in hospitalized pediatric patients for various hemato-oncological diseases ± HSCT. A survey of respiratory viruses was done using direct immunofluorescent antibody assay from nasopharyngeal washing aspirate. Results: In two RSV infection outbreaks (2006 and 2009), RSV antigen was detected in 6/30 patients. Five of six patients with RSV antigen were all treated with 0.2–0.4 g/kg intravenous immune globulin (IVIG) and specific antiviral therapy, oral ribavirin (20–25 mg/kg/day in three doses). Five patients recovered fully, although two were retreated due to recurrent (+) RSV antigen and respiratory symptoms within 2 weeks. We did not give oral ribavirin to one patient with (+) RSV antigen due to mild symptoms. All patients are alive and well. Conclusions: In contrast with the outcome of RSV infection in adult oncology patients, the mortality associated with RSV infection in pediatric oncology patients even in post bone marrow transplantation (BMT) period, is low when diagnosed and treated early enough. Oral ribavirin might be an option together with IVIG in the treatment of RSV especially when other forms of antivirals could not be obtained. This approach will make it possible to give the scheduled anti-neoplastic therapy on time. **Pediatr Pulmonol. 2010; 45:307–311.** © 2010 Wiley-Liss, Inc.

Key words: respiratory syncytial virus; pediatric oncology patients; oral ribavirin.

INTRODUCTION

Respiratory syncytial virus (RSV) is a single-stranded, enveloped RNA virus of the paramyxovirus family, which represents the major cause of serious lower respiratory tract infection in children less than 2 years of age. Multiple factors including mucosal barrier, fever, local inflammatory response, α and β interferon, nonspecific phagocytosis and humoral and cellular immune response contribute to resistance to infection and recovery from infection. Chemotherapy leads to mucositis in immunocompromised children with cancer, with loss of integrity in the mucosa and immunoglobulin (Ig)A impairment. The low production of serum antibodies, deficient cytotoxic T-cell function, neutropenia and lymphopenia increases the risk of infection in lower airway.[1,2] Immunocompromised hematological patients are at high risk for severe, often fatal RSV pneumonia.[3,4] Once pneumonia develops, overall mortality is 60–80%, regardless of the treatment strategy.[3] There have been few reports describing the outcome of RSV infection specifically among pediatric oncology patients.

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Ribavirin is a synthetic nucleoside analogue with a broad spectrum activity against RNA and DNA viruses.[5–7] Currently, it is approved only as aerosol therapy in small children with severe RSV pneumonia, but it is also used orally in various clinical trials in chronic hepatitis C. There are only three studies concerning the use of oral ribavirin

[1]Department of Pediatric Hematology/Oncology/BMT, Istanbul School of Medicine, Istanbul University, Istanbul, Turkey

[2]Department of Pediatric Hematology, Okmeydani Education and Research Hospital, Istanbul, Turkey

[3]Department of Pediatric, KSU Medical School, Kahramanmaras, Turkey

*Correspondence to: Kartaltepe mah. Dost sok. Motif apt. No:5 D:11, Bakirkoy-Istanbul 34144, Turkey. E-mail: didematay@hotmail.com

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in viral respiratory tract infections in HSCT patients.[8–10] However, the efficacy and required oral dose of ribavirin in HSCT are uncertain but has a bioavailability of 30–74%.[11]

We report our experience during an outbreak of RSV infection in a pediatric hemato-oncology ward at a tertiary care hospital, which we utilized oral ribavirin and IVIG treatment successfully.

CASE REPORT

Two RSV infection outbreaks developed in hospitalized pediatric patients for various hemato-oncological diseases treated with or without HSCT between February–April 2006 and January–March 2009. Fourteen of 30 patients developed rhinorrhea, progressive cough and/or dyspnea in these two time periods.

RSV antigen was detected in six patients [high-risk ALL receiving induction therapy, standard risk ALL on consolidation chemotherapy (CT); three patients receiving high-dose chemotherapy for relapsed ALL, stage IV neuroblastoma, and relapsed Hodgkin's disease, respectively, and one with hyper IgM syndrome-post-BMT under treatment for chronic GvHD].

All RSV antigen positive patients had lower respiratory tract infection. None of them was associated with fever at the time of diagnosis. Four patients were severely neutropenic and two patients were not neutropenic but immunosuppressed because of their chronic GvHD and treatment.

Patient 1—index case—is a 2-year-old girl, who was under consolidation chemotherapy for standard risk ALL. She was admitted to the hospital with a productive cough. After RSV was identified in this patient, all in-patients in the same ward were screened for RSV disease. A survey of respiratory viruses was done by using direct immunofluorescent antibody assay from nasopharyngeal washing aspirate. Nasopharyngeal washings were collected by nasopharyngeal suctioning into a sterile cup and transported on wet ice to the virology laboratory within 2 hr.

In 2009, RSV RNA was assessed in 15 patients with or without symptoms using PCR and was positive in 9 of 15 patients. Two of these patients were asymptomatic and RSV antigen was positive in 3/9 patients with symptoms. The remaining patients with respiratory symptoms in either outbreak periods were closely tested for development of a RSV infection, but remained negative during all surveys. RSV-related clinical characteristics were reviewed and are summarized in Tables 1 and 2.

Patients with RSV infection were isolated from other immunocompromised patients to prevent nosocomial transmission. Contact precautions including isolation of infected patients, hand washing and wearing masks and gloves were applied. The RSV positive patients were checked weekly for RSV antigenemia and with chest radiographs. All patients were treated with parenteral antibiotics for concurrent infections of presumed bacterial origin. Twenty-six days after the diagnosis of RSV infection, *Escherichia coli* was isolated from one patient's blood culture (patient 2, Table 1).

Five of six patients with documented RSV antigen positivity, and the sister (RSV antigen was negative) of the boy with hyper-IgM syndrome and RSV antigen positivity who was status post HSCT and under treatment for chronic GvHD and pneumonia were all treated with 0.2–0.4 g/kg intravenous immune globulin (IVIG) and oral ribavirin (20–25 mg/kg/day in two to three doses) till 2 weekly negative RSV antigen test results. Oxygen and salbutamol were also administered when hypoxia and wheezing were detected due to reactive airway disease secondary to RSV. The duration of RSV positivity has been prolonged in our patients (Tables 1 and 2).

Six patients recovered fully, although two were retreated due to recurrence of RSV antigen positivity and respiratory symptoms within 2 weeks. We did not give oral ribavirin to one patient with a (+) RSV antigen due to mild symptoms. All patients are alive.

DISCUSSION

General recommendations for RSV infections in cancer are strict infection control measures, delaying chemotherapy or BMT, treatment with aerosolized ribavirin plus high-dose IVIG in both adults and children.[3,12–14] According to the literature there are different recommendations for ribavirin treatment in oncology patients, such as aerosolized, i.v. or oral applications, but no treatment option was also suggested frequently.[15,16]

In adults, Ebbert et al. reported their experience in 11 immunocompromised patients with RSV pneumonitis. Five of the 11 patients survived this infection while all of the patients who were mechanically ventilated and did not receive ribavirin therapy died of respiratory failure.[1] Harrington et al.[17] reported a mortality rate of 100% in bone marrow transplant patients who developed RSV pneumonitis and did not receive ribavirin therapy.

On the other hand, in an open-label pilot trial of Ghosh et al.[3] prompt treatment of RSV in BMT recipients with aerosolized ribavirin and IVIG was found to be safe and associated with less mortality and less occurrence of pneumonia. Schleuning et al.[12] found that intravenous ribavirin was effective in controlling RSV infections in recipients of BMT. Anaissie et al.[15] suggested that cancer patients with RSV may not necessarily suffer severe respiratory complications when undergoing chemotherapy, even in the absence of RSV-specific therapy. Delaying chemotherapy in such patients may not be necessary. In Khanna et al.[10] study, oral ribavirin, intravenous immunoglobulin, and palivizumab were used in 34 oncologic patients with severe immunodeficiency. Because of heterogeneous therapy combinations, small sample size,

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TABLE 1— Patient Summary, 2006

Patients, n = 15	Diagnosis	BMT	Ongoing therapy	Symptom	RSV antigen	Therapy (ribavirin + IVIG)	RSV antigen positivity
1	ALL (SR) index case	−	Consolidation chemotherapy	Cough, pneumonia	+	+	4 weeks
2	ALL (HR)	−	Late consolidation chemotherapy	Cough, pneumonia	+	+	7 weeks
3	Hyper IgM	+	Chronic GvHD	Cough	+	+	3 weeks
4	Hyper IgM	+	Chronic GvHD	Cough, pneumonia	−	+	—
5–7	ALL	−	Various	Cough	−	−	—
8–15	Various malignancies	1 CML +	Various	—	−	−	—

and a retrospective context, they were unable to provide a conclusion regarding whether oral ribavirin therapy affected outcome. However, they suggested that oral ribavirin therapy is probably comparable to aerosolized ribavirin therapy.

Among pediatric oncology patients, morbidity and mortality related to RSV infection is not known. There are few reports including children with cancer. In these patients, RSV infection appears to result with a lower mortality rate, with or without specific antiviral therapy. Koskenvuo et al. found evidence of respiratory viral infection in 44% of the febrile episodes in children with leukemia. Rhinovirus (22%) and RSV (11%) were the most frequently detected viruses.[18] Children with RSV infections were alive and well without specific antiviral treatment. Cole et al.[16] suggested that specific antiviral therapy be reserved for only those patients with high risk because of comorbidities. They described 18 pediatric patients being actively treated with chemotherapy with a diagnosis of RSV infection. Nine episodes of RSV infections (50%) were treated with ribavirin. Seven patients (39%) had documented concurrent infection with one or more organisms. There were no deaths due to RSV infection and no intensive care admission was needed because of the RSV infection. On the other hand, Vettenranta et al. reported six cases of RSV infection in children. Their experience indicated that promptly administered ribavirin might be beneficial in slowing or even terminating the progress of the infection in severely neutro/lymphopenic patients prior to marrow recovery.[19] Hall et al.[20] reported 20 pediatric oncology patients and RSV with a 100% incidence of lower respiratory tract infection (LRI), 60% intensive care treatment and 15% mortality. In 2008, Children's oncology group (COG) emphasized that, children with acute myeloid leukemia, who experience RSV infections are at high risk of RSV related mortality (10%).[21]

Palivizumab (PVZ) is a humanized monoclonal antibody directed against the F (fusion) protein of RSV. It is recommended for prophylaxis of severe RSV infection in high risk children.[22] But Children's Oncology Group (COG) report does not support routine administration of PVZ to prevent RSV infection.[21] The role of concomitant intravenous immunoglobulin or RSV-specific immunoglobulin or PVZ for the treatment of RSV related LRIs is poorly defined. Chavez et al.[23] have shown favorable results with combination therapy with ribavirin and i.v. PVZ. But there is no consensus on the role of antibody preparations.

In our experience; pediatric oncology patients with RSV infections, even in post-BMT period were treated with a successful outcome when IVIG and oral ribavirin were administered early. It is even possible to give the scheduled anti-neoplastic therapy in order to prevent a delay in oncological therapy. Aerosolized ribavirin may be teratogenic, and pregnant staff should be prohibited to enter the ward. Side effects like bronchospasm, nausea, worsening of cough have been reported with aerosolized ribavirin treatment. Our choice of oral ribavirin and IVIG was mainly due to lack of other application facilities and drugs.

It is very important to detect RSV infection rapidly in a hematology/oncology ward for limiting nosocomial spread of infection, because prolonged shedding and LRI are common in children. Nasopharyngeal antigen detection through IFA is rapid and reliable compared to cultivation of RSV. However, negative tests must be repeated if the patient's symptoms persist. RSV antibody detection is mostly useless because of the inadequate antibody production. Because RSV is highly contagious and may spread rapidly throughout the unit, contact precautions for patients with symptoms of upper respiratory tract infections until RSV antigen is negative, wearing mask and gloves by every contact and hand washing are very important for controlling the infection.

RSV infections among patients with hematological malignancy are associated with a more prolonged duration (RSV shedding may exceed 100 days versus 21 days for immunocompetent children), with a higher rate of pneumonia, co-pathogens and death. In our findings, one patient tested positive for RSV antigen for 7 weeks, two patients had pneumonia, and two were retreated due to recurrent RSV positivity and respiratory symptoms within 2 weeks.

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TABLE 2—Patient Summary, 2009

Patients, n = 15	Diagnosis	BMT	Ongoing therapy	Symptom	RSV antigen	RSV RNA	Therapy (Ribavirin + IVIG)	RSV antigen positivity
1	Neuroblastoma, stage IV (index case)	−	Consolidation chemotherapy	Cough, pneumonia, diarrhea	+	+	+	2 weeks
2	NHL	−		Cough	−	+	−	
3	ALL (HR)	−			−	+	−	
4	Relapsed NHL	−			−	+	−	
5	Relapsed Neuroblastoma	+	Late consolidation chemotherapy	Cough	−	+	−	
6	Relapsed Neuroblastoma	−	Chronic GvHD	Cough	−	+	−	
7	Relapsed HD	−	Chronic GvHD	Cough	+	+	−	2 weeks
8	Relapsed ALL	−	Various	Cough	−	+	−	—
9	Relapsed AML	+	Various	Cough, pneumonia	+	+	+	2 weeks
10–15	Various malignancies	−		—	−	—	−	

In conclusion, recovery of RSV infection in pediatric high-risk oncology patients is possible when they are treated early enough with ribavirin and IVIG. Oral ribavirin therapy is safe and practical. Also infection control measurements are effective to protect other patients from RSV outbreak. When RSV related LRI was suspected, we recommend treating high-risk patients even when they are negative for RSV. Also the laboratory should be alerted for repeated RSV antigen and RSV cultivation to diagnose suspicious cases. The mortality rate of RSV infection in children seems to be less when compared to the adults. Our data is limited, so further studies are needed in pediatric oncology cases to determine the efficacy of oral ribavirin in RSV infections.

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